Agarwal *et al. Egyptian Liver Journal* (2024) 14:27
https://doi.org/10.1186/s43066-024-00333-8

Egyptian Liver Journal

CASE REPORT

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Cholestatic liver injury secondary to over-the-counter cyproheptadine: case report and review of literature

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Abstract

Background Cyproheptadine is an easily available over-the-counter first-generation antihistaminic that is often used as an appetite stimulant. Although it is usually a safe drug, rare instances of drug-induced liver injury may occur.

Case presentation We report a case of cholestatic liver injury secondary to cyproheptadine in a young pharmacy student with chronic hepatitis B and review the literature of cyproheptadine-induced liver injury.

Conclusion Although cyproheptadine is largely a safe drug, its potential for significant liver toxicity cannot be ignored.

Keywords Cyproheptadine, Drug-induced liver injury, Cholestasis, Orexigenic

Background

Cyproheptadine is a first-generation antihistaminic drug initially introduced as an antipruritic agent which has gained much popularity because of its orexigenic and appetite-stimulating effects [1]. Easy over-the-counter availability makes it an alluring agent among adolescents and young adults concerned about their body image. Although it is generally considered a safe drug, rare instances of liver injury may occur [2]. We present a case of a young male with cholestatic liver injury secondary to cyproheptadine and review the associated literature.

Case report

A 20-year-old male pharmacy student presented to the liver clinic of a teaching hospital in northern India with a history of progressive jaundice of 1-month duration which was associated with pruritus and clay-colored stools. There was no history of prodrome, pain, fever, abdominal distension, or gastrointestinal bleeding. He was a teetotaler with no history of drug abuse or unsafe sexual practices. At the index presentation to the primary physician, he was diagnosed with Hepatitis B (details of liver function and viral workup were not available), for which he was started on tenofovir. He was subsequently referred to us for consultation in view of worsening jaundice 3 weeks later. The patient admitted to over-the-counter use of cyproheptadine (20 mg per day) to gain weight for a period of 3 months, which he stopped on noticing yellowish discoloration of urine. On physical examination, there was icterus, scratch marks over the trunk and extremities, shiny nails, and a firm hepatomegaly with a liver span of around 16 cm. Investigations revealed that hemogram and other routine biochemical parameters were normal except for deranged liver function tests (total bilirubin, 15.3 mg/dL; direct bilirubin, 9.6 mg/dL; AST, 66 IU/L; ALT, 82 IU/L; ALP, 346 IU/L; GGT, 180 U/L). Virological workup showed HBV-DNA of 4.8×10^4 IU/mL with positive HBeAg antigen and negative IgM anti-HBc antibody. Serologies for Hepatitis A, C, and E, cytomegalovirus, herpes simplex virus, and

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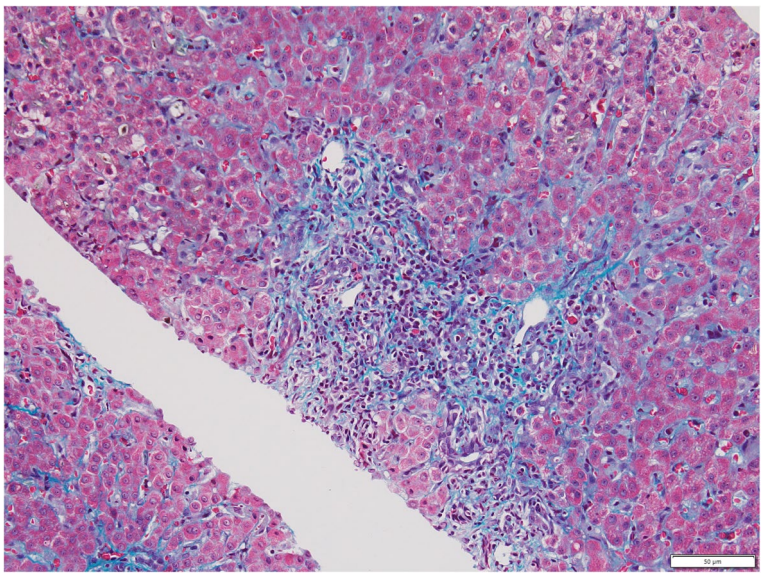

Fig. 1 Occasional portal tracts show fibrotic expansion and incomplete septa

autoimmune workup (including anti-mitochondrial antibody) were negative. Serum ceruloplasmin levels were normal (32 mg/dL). Ultrasound abdomen and MRCP corroborated hepatomegaly and did not reveal any biliary pathology. As the clinical presentation and biochemical profile of the patient were not explainable by Hepatitis B alone, a liver biopsy was performed keeping a possibility of cholestatic drug-induced liver injury secondary to cyproheptadine with an R score of 0.7.

The biopsy revealed mild portal and occasional portoseptal fibrosis with variable degrees (mild to moderate) of inflammation comprising of lymphocytes, a few plasma cells, neutrophils, and eosinophils (Fig. 1). No interface activity was noted. Occasional interlobular bile ducts showed degenerative cholangiocyte changes. A mild ductular reaction was noted (Fig. 2). The hepatic lobules showed centrizonal cholestasis along with lobular disarray and feathery degeneration (Fig. 3). CK7 immunostain highlighted occasional biliary metaplasia. Multiple foci of lobular inflammation (4–10/10 × field) were seen. The hepatocytes also showed occasional HBcAg nuclear positivity (Fig. 4). The overall histopathological pattern suggests a chronic hepatitis pattern, likely resulting from chronic hepatitis B (modified HAI score

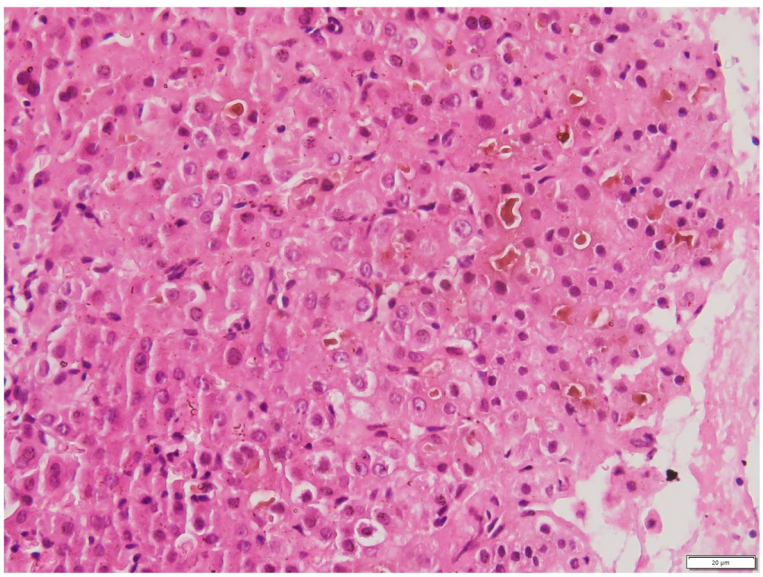

Fig. 2 Hepatic lobules showing centrizonal cholestasis and feathery degeneration

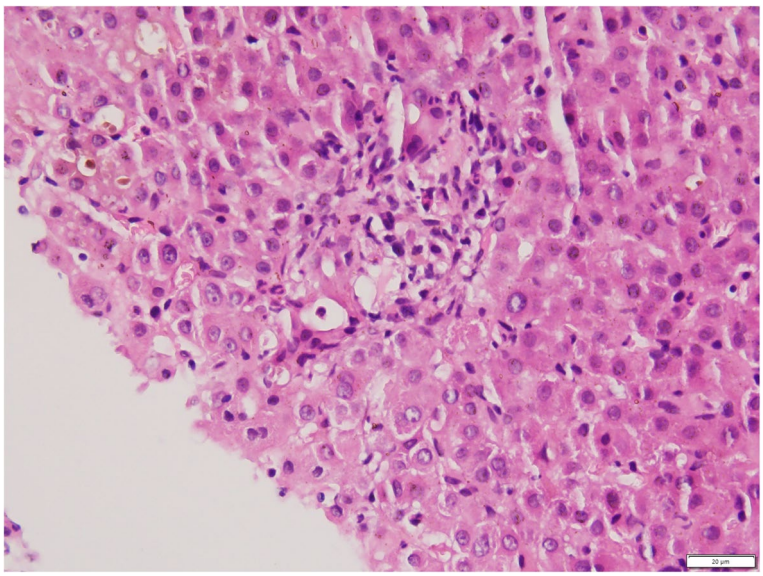

Fig. 3 Occasional interlobular bile ducts showing degenerative changes in the cholangiocytes and ductular reaction

0 + 0 + 3 + 2 = 5/18; fibrosis stage 2) with superimposed centrizonal cholestasis, occasional degenerative changes in the ductal cholangiocytes, and portal eosinophilic sprinkling, likely related to a cholestatic-drug induced liver injury (cholestatic-DILI). Thus, the final diagnosis was consistent with cyproheptadine-induced cholestatic liver injury on a background of chronic Hepatitis B.

He was managed conservatively with ursodeoxycholic acid, cholestyramine, and naltrexone. Gradually, his pruritus and jaundice improved with normalization of liver function parameters at 8 weeks of follow up.

Discussion

Cyproheptadine is considered to be a safe drug with mild neurological manifestations such as sedation being the most frequently reported adverse effects. However, drug-induced liver injury manifesting as mixed or cholestatic hepatitis may rarely occur with an estimated frequency of 0.27–1.4 per 1000 patients [3]. Clues to the mechanism of hepatotoxicity of cyproheptadine can be gleaned from an analysis of its chemical structure. The tricyclic ring structure of cyproheptadine is analogous to phenothiazines like the antipsychotic chlorpromazine, the hepatotoxic

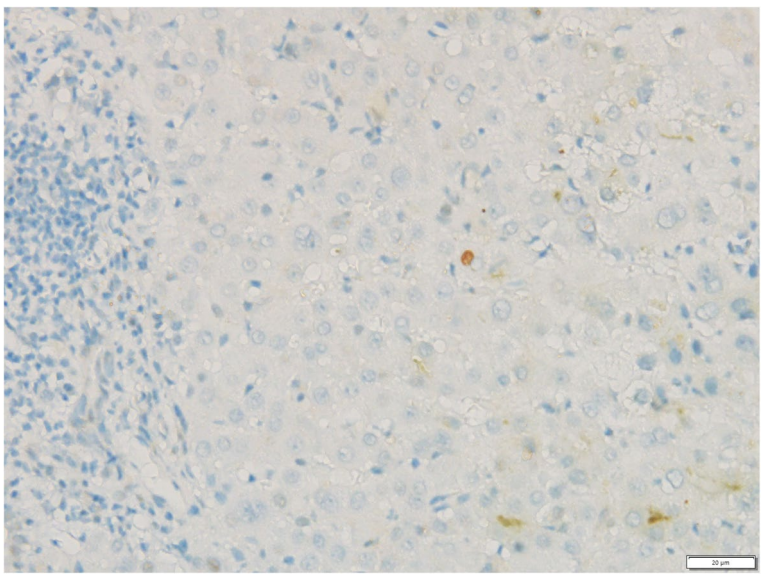

Fig. 4 Occasional HBcAg nuclear positivity in the hepatocytes

Table 1 Review of literature depicting case reports and series of cyproheptadine-induced liver injury

Study	Age/sex	Indication	Dosage	Pattern of liver injury	Potential confounders	Temporal evolution
Henry et al. [5]	25/F	Pruritus	12 mg/day	Cholestatic	None	Onset of jaundice after drug initiation: 1 month; Resolution of jaundice after drug discontinuation: 2 months
Larrey et al. [3]	23/F	Anorexia	12 mg/day	Cholestatic	Acetylsalicylic acid, ethinylestradiol, quingestrone	Onset of jaundice after drug initiation: 5 days; Resolution of jaundice after drug discontinuation: 3 weeks
Freneaux et al. [6]	Adult (NA)	Appetite stimulation	8 mg/day	Cholestatic	Dihydroergocristine, magnesium + pyridoxine, methionine + cysteine	Onset of jaundice after drug initiation 1 month; Resolution of jaundice after drug discontinuation: 3 months
Chertoff et al. [2]	55/F	Appetite stimulation	NA	Acute liver failure	None	Onset of jaundice after drug initiation: 3 weeks; Resolution of jaundice after drug discontinuation: 3 weeks
Garland et al. [7]	40/F	"Figure enhancer"	NA	Drug-induced autoimmune hepatitis (hepatocellular)	Lysine, alcohol	Onset of jaundice after drug initiation: 6 weeks; Resolution of jaundice after drug discontinuation: 3 months
Bertrand et al. [1]	15 patients (1–94 years)	Orexigenic in 2 Non available in 13	Ranging from 4 to 12 mg/day	Hepatocellular, cholestatic, acute liver failure in 3	-	-
Our case	20/M	Orexigenic	20 mg	Cholestatic	Chronic hepatitis B	Onset of jaundice after drug initiation: 3 months; Resolution of jaundice after drug discontinuation: 2 months

potential of which is well known [3]. Decoupling of oxidative phosphorylation has also been speculated as a potential mechanism due to the presence of a tertiary amine. Studies in rats suggest that cyproheptadine can induce an ultrastructural change in hepatocytes with an increase in microsomal cytochrome P450 enzyme [4].

Clinical data on drug-induced liver injury secondary to cyproheptadine is scant and is largely confined to case reports and series as shown in Table 1. The largest series comes from a French national pharmacovigilance database study from 1985 to 2020 which recorded a total of 15 cases of liver injury suspected to be secondary to cyproheptadine including three patients with cholestatic hepatitis [1]. Three other patients have also been published in case reports. Importantly the French national pharmacovigilance study reported acute liver failure in four patients. Thus it becomes necessary to be aware and vigilant about the potential hepatic adverse effects of this seemingly safe drug which is readily available over the counter in India. This would be particularly prudent in a patient with pre-existing liver disease as in our pharmacy student with chronic Hepatitis B.

Fortunately, most cases in the literature resolve with conservative management after withdrawal of cyproheptadine within 1–3 weeks. However, cholestatic hepatitis may take longer to resolve (as seen in the index case) with a reported duration of 3 to 32 weeks.

Conclusion

Although cyproheptadine is largely a safe drug, its potential for significant liver toxicity cannot be overlooked. Clinicians should be cognizant of this while prescribing cyproheptadine particularly in patients with pre-existing chronic liver disease.

Abbreviations

AST	Aspartate transaminase
ALT	Alanine transaminase
ALP	Alkaline phosphatase
GGT	Gamma-glutamyl transferase
DILI	Drug-induced liver injury
CK7	Cytokeratin 7
HAI	Histology activity index
MRCP	Magnetic resonance cholangiopancreatography

Acknowledgements
None to declare.

Authors' contributions
All authors have contributed equally to the manuscript.

Funding
This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Verbal and written informed consents were given by the patient's wife for the publication of this case. A copy of written consent is available for the journal.

Competing interests
The authors declare that they have no competing interests.

Received: 25 November 2023 Accepted: 18 April 2024
Published online: 24 April 2024

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